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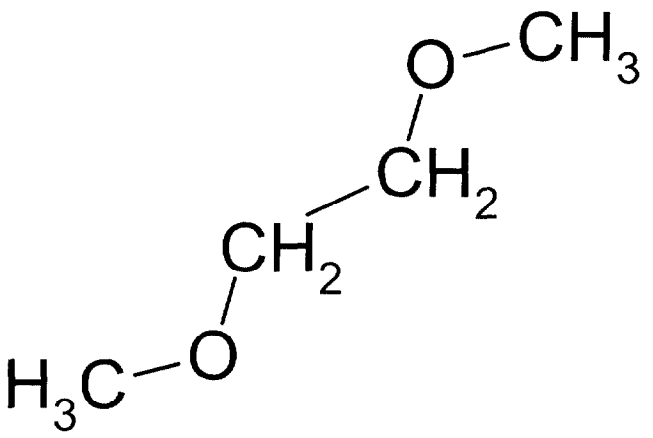

# 1,2-Dimethoxyethane

**CAS Number 110-71-4**

## U.S. EPA HPV Challenge Program Submission

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Submitted on behalf of
Ferro Corporation

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# Table of Contents

Executive Overview ..... 4
Testing Plan and Rationale ..... 5
Testing Plan in Tabular Format ..... 6
Introduction ..... 7
Physical-chemical Data ..... 8
*Available Information* ..... *8*
*Summary and Recommendation for Physical-Chemical Data:* ..... *9*
Environmental Fate and Pathways ..... 9
*Biodegradation* ..... *9*
*Photodegradation* ..... *9*
*Water Stability* ..... *9*
*Distribution* ..... *9*
*Summary and Recommendations for Fate* ..... *10*
Ecotoxicity ..... 10
*Aquatic Toxicity* ..... *10*
*Summary and Recommendation for Aquatic Toxicity:* ..... *11*
Acute Toxicity ..... 11
*Oral Exposure* ..... *11*
*Inhalation Exposure* ..... *11*
*Summary and Recommendation for Acute Toxicity* ..... *12*
Repeat Dose Toxicity ..... 12
*Figure 1. Metabolism of 2-Methoxyethanol into Methoxy Acetic Acid.* ..... *13*
*Oral Exposure* ..... *14*
*Figure 2. Major Metabolic Pathways for Monoglyme* ..... *15*
*Summary and Recommendations for Repeated-Dose Toxicity* ..... *15*
Genetic Toxicity ..... 16
*Genetic Toxicology in vitro* ..... *16*
*Summary of Genetic Toxicology and Recommendations:* ..... *17*
Reproductive Toxicity ..... 17
*Summary and Recommendation for Reproductive Toxicity* ..... *17*
Developmental Toxicity ..... 17
*Summary and Recommendation for Developmental Toxicity* ..... *18*
Conclusions ..... 19
References ..... 19
Robust Summaries ..... 22
Physicochemical Properties ..... 23
*Melting Point* ..... *23*
*Boiling Point* ..... *24*
*Vapor Pressure* ..... *25*
*Partition Coefficient, Octanol-Water* ..... *26*
*Water Solubility* ..... *27*
Fate ..... 28
*Photodegradation* ..... *28*
*Water Stability* ..... *29*

*Theoretical Distribution (Fugacity)* ..... *31*
*Biodegradation* ..... *34*
Effects on Environmental Organisms ..... 37
*Acute Toxicity to Fish* ..... *37*
Type ..... 37
*Acute Toxicity to Aquatic Invertebrates* ..... *43*
*Acute Toxicity to Aquatic Invertebrates, Supporting Study* ..... *47*
*Toxicity to Aquatic Plants* ..... *49*
*Toxicity to Aquatic Plants (model validation study)* ..... *50*
Acute Health Effects ..... 57
*Acute Oral Toxicity* ..... *57*
*Acute Inhalation Toxicity* ..... *60*
Repeated Dose Toxicity, ..... 64
*Rat Thirteen-Week Drinking Water* ..... *64*
*Repeated Dose Toxicity, Mouse Thirteen-Week Drinking Water* ..... *68*
Genetic Toxicology ..... 72
*Chinese Hamster Ovary Cell Mutation Test (HGPRT)* ..... *72*
*Sister Chromatid Exchange in Chinese Hamster Ovary Cells (SCE Test)* ..... *75*
*In Vitro Unscheduled DNA Synthesis (UDS) Assay* ..... *78*
Reproductive Toxicology ..... 81
*Screening Study in Mice* ..... *81*
Developmental Toxicology ..... 84
*Developmental Toxicology, Oral* ..... *84*
*Developmental Toxicology, Oral, Mouse* ..... *91*

# Executive Overview

1,2-Dimethoxyethane (CAS Number 110-71-4, Monoglyme) is a stable diether used primarily as an industrial solvent, process aid and as a component of lithium batteries.

The physical-chemical properties of Monoglyme are well defined. It is a volatile liquid at room temperature with a vapor pressure of 54 mm Hg. Monoglyme is poorly biodegradable in a waste water treatment facility and not considered readily biodegradable. It has high hydrolytic stability in water at pH 4 to 9 with an estimated hydrolytic half-life at 25˚ C greater than one year. Vapors have an estimated photolytic half-life in air of approximately 8 hours, and predicted values for fugacity have been calculated with the Mackay Level III model. Based on surrogate materials and a validated SAR relationship, fish, daphnia and green algae are estimated to be acutely affected by Monoglyme only at concentrations far in excess of 1000 mg/l. Acute toxicity to mammals has been determined by oral and inhalation routes of exposure. Monoglyme demonstrates a low order of toxicity with an oral $LD_{50}$ of greater than 4000 mg/kg in rats. Standard repeated-dose studies have not been conducted; however, the spectrum of toxicity can be confidently predicted from Monoglyme's metabolism and studies on related compounds by all routes of exposure. Toxic responses include thymic atrophy, bone marrow suppression and testicular degeneration. Genotoxicity has been evaluated using multiple *in vitro* experimental procedures covering both mutation and chromosomal aberration. Results of genotoxicity studies are mixed. Adverse effects to reproduction are based on metabolism of Monoglyme to 2-methoxy acetic acid, a compound that is known to interfere with sperm production. Developmental toxicity results are available and, as expected from its structure, Monoglyme appears to be a specific developmental toxin in rats and mice.

With regard to the HPV program, no additional testing is proposed for Monoglyme, as all required parameters are sufficiently well characterized by available information.

# Testing Plan and Rationale

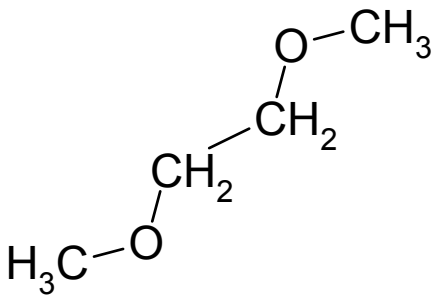
## Testing Plan in Tabular Format

| CAS Number 110-71-4<br>1,2-Dimethoxyethane | Information Available? | OECD Study ? | GLP Study? | Other Information ? | Estimation Method? | Acceptable? | Testing Recommended? | |
|---|---|---|---|---|---|---|---|---|
| **HPV Endpoint** | | | | | | | | |
| **Physical Chemical** | | | | | | | | |
| Melting Point | Y | N | N | Y | N | Y | N | |
| Boiling Point | Y | N | N | Y | N | Y | N | |
| Vapor Pressure | Y | N | N | Y | N | Y | N | |
| Partition Coefficient | Y | N | N | N | Y | Y | N | |
| Water Solubility | Y | N | N | N | N | Y | N | |
| **Environmental & Fate** | | | | | | | | |
| Photo-Degradation | Y | N | N | N | Y | Y | N | |
| Water Stability | Y | N | N | Y | Y | Y | N | |
| Transport | Y | N | N | N | Y | Y | N | |
| Biodegradation | Y | N | N | Y | N | Y | N | |
| **Ecotoxicity** | | | | | | | | |
| 96-Hour Fish | Y | N | N | N | Y | Y | N | |
| 48-Hour Invertebrate | Y | N | N | N | Y | Y | N | |
| 72-Hour Algae | Y | N | N | N | Y | Y | N | |
| **Toxicity** | | | | | | | | |
| Acute | Y | N | N | Y | N | Y | N | |
| Repeated Dose | Y | Y | Y | Y | Y | Y | N | |
| Genetic Toxicology *in vitro* | Y | Y | N | Y | N | Y | N | |
| Genetic Toxicology *in vivo* | Y | N | N | N | N | Y | N | |
| Reproductive | Y | N | N | Y | N | Y | N | |
| Developmental | Y | N | N | Y | N | Y | N | |

(Y = Yes, N = No)

## Introduction

1,2-Dimethoxyethane, CAS Number 110-71-4 (Monoglyme) is the dimethyl ether of ethylene glycol. It is a clear volatile liquid that is miscible with water and most organic solvents. Its primary use is as a solvent; the structure is shown below:




1,2-Dimethoxyethane has been in industrial use for about 40 years it is also known as:

- Monoglyme
- Glyme
- Dimethoxyethane
- Dimethyl cellosolve
- Ethylene glycol dimethyl ether

The chemical and physical properties of Monoglyme make it a unique solvent for certain applications. (1) It is a preferred solvent in the production of Lithium batteries because of its low viscosity and cation solvating property. Likewise as an industrial reaction solvent, it facilitates certain reactions including use as a solvent to facilitate formation of alkali metal-hydrocarbon adducts; in the Reformatsky reaction with methyl gamma-bromocrotonate (2)

Its high solvent power, low viscosity and volatility make it useful in some industrial coating applications. Consumer applications of Monoglyme are discouraged because of the known reproductive and developmental toxicity of lower molecular weight alkyl glycol ethers such as monoglyme. Domestic use of Monoglyme is between one and two million pounds per year and worldwide production use could be as high as six million pounds per annum. The manufacturers

estimate that 10 to 20 percent of the US production is used in the domestic production of Lithium batteries.

Exposure in these applications is limited by process controls and protective equipment there is no occupational exposure level set by governmental agency, except in Russia where there is a STEL of 10 mg/$m^3$. (1) Ferro Corporation recommends a Threshold Limit Value for glycol ethers of 5 ppm (TWA) with a Short Term Exposure Limit (STEL) of 25 ppm. The 15-minute STEL should not be achieved more than 4 times in 8 hours. For women of child-bearing potential, Ferro recommends a TLV of 1 ppm with s STEL of 5 ppm. (3)

Several studies have been conducted on the toxicity of Monoglyme. These studies are briefly reviewed in this rationale document describing how they meet the SIDS (Screening Information Data Set) end-points of the United States Environmental Protection Agency (USEPA) High Production Volume Challenge Program (HPV). Robust summaries have been prepared for key studies; supporting studies are referenced in these summaries. Specific additional testing is recommended to fill the remaining end-points of the SIDS data set. (or rationale is provided why certain end-point do not have to be filled)

## Physical-chemical Data

### Available Information

Physical-chemical data for Monoglyme are available from the literature and company sources.

| | |
|---|---|
| Melting Point | -58° C (4)<br>-69˚ C (Ferro book)<br>-71˚ C (HSDB alternative) |
| Boiling Point | 85 deg C @ 760 mm Hg (5) |
| Vapor Pressure | 48 mm Hg @ 20˚ C (6)<br>54 mm Hg @ 20˚ C (1) |
| Partition Coefficient | Log $K_{o/w}$ = -0.21 (7) |
| Water Solubility | Soluble in all proportions (4) |

These properties indicate that Monoglyme is a volatile liquid with high water solubility. The value of the partition coefficient suggests that Monoglyme will partition into water and has little potential for bioaccumulation.

**Summary and Recommendation for Physical-Chemical Data:**

All information required by the HPV Program is available. No additional studies are recommended.

## Environmental Fate and Pathways

### Biodegradation

Biodegradation has received limited attention. In a recent publication, Cowan and Kwon (8) describe a series of biodegradation studies on several ethylene glycol ethers. Using a high concentration of acclimated bacterial, initially obtained from a petroleum refinery wastewater treatment plant, they were unable to detect significant biodegradation of Monoglyme. This result is supported by three earlier publications that reported Monoglyme was recalcitrant to biodegradation, has questionable biodegradation, or is not assimilated as a substrate by bacteria. (9,10,11)

### Photodegradation

Photodegradation was estimated using version 1.90 of the Atmospheric Oxidation Program for Microsoft Windows (AOPWIN) that estimates the rate constant for the atmospheric, gas-phase reaction between photochemically produced hydroxyl radicals and organic chemicals. The estimated rate constant is used to calculate atmospheric half-lives for organic compounds based upon average atmospheric concentrations of hydroxyl radical. An experimentally derived rate constant is listed in the APOWIN program. Using the default atmospheric hydroxyl radical concentration in APOWIN and the measured rate constant for reaction of Monoglyme with hydroxyl radical, the estimated half-life of Monoglyme vapor in air is approximately 8 hours (12).

### Water Stability

Ethers are established to be relatively or completely inert in water as are glycols (13). Experience with Monoglyme in various aqueous preparations supports its resistance to hydrolysis under conditions that would occur in the environment.

### Distribution

Theoretical Distribution (Fugacity) of Monoglyme in the environment was estimated using the Mackay Level III model with measured values for physical and fate constants were available

and standard defaults in EPIWIN v 3.05 (14). The results for distribution using a model calculated Ko/c (adsorption coefficient based on organic carbon content) of 0.253 are:

- Air 0.91 %
- Water 61 %
- Soil 38 %
- Sediment 0.1 %

**Summary and Recommendations for Fate**

Monoglyme is resistant to hydrolysis and biodegradation by acclimated bacteria. The EQC Level III model suggests it will distribute primarily to water. Environmental degradation to carbon dioxide will likely occur by a combination of slow biodegradation and reaction with atmospheric hydroxyl radicals after volatilization. All fate parameters have adequate information to fulfill the HPV Program requirements. No further testing is recommended.

## Ecotoxicity

**Aquatic Toxicity**

No studies of aquatic toxicology were found. EPIWIN estimates, using the neutral organic model are given in the table below.

| EPIWIN Aquatic Toxicity Estimates, Monoglyme (15) | |
|---|---|
| Fish, 96 hour $LC_{50}$ | 7984 mg/L |
| Daphnia, 48 hour $EC_{50}$ | 7344 mg/L |
| Algae, 96 hour $EC_{50}$ | 4042 mg/L |

These estimates are supported by fish and invertebrate data for Diglyme that reveals $LC_{50}$ and $EC_{50}$ values in the same range as that predicted for Monoglyme by the modeling program (16). Other surrogate chemicals, 1,3-Dioxolane for fish and daphnids (17) and 2-Methoxyethanol for daphnids (18), also demonstrate acute toxicity in this same range providing support for the estimated values for Monoglyme. The data from Diglyme for acute fish toxicity $LC_{50} > 2000$ mg/L, which has terminal methoxy groups similar to the structure of Monoglyme, indicate that the methoxy groups are not specifically toxic toward fish.

The algae ESOSAR result of 4042 mg/L is considered satisfactory for the HPV program since the model has been validated by a high-reliability study on a similar compound. The validation (surrogate) study is presented it the attached robust summary for this endpoint.

**Summary and Recommendation for Aquatic Toxicity:**

Modeling and comparison with related compounds indicate that Monoglyme is of low concern to aquatic environmental species. Given that the estimates and surrogate compounds show acute toxicity parameters several fold the OECD recommended maximum concentration for these studies, there is a high degree of confidence that Monoglyme is of similar low hazard. Modeling results of algae data based on the ECOSAR mode are sufficient for the purpose of the HPV program. No further testing is recommended.

## Acute Toxicity

**Oral Exposure**

The acute oral LD50 for rats has been determined in at least two studies. The critical study chosen for preparing a robust summary gives the LD50 as > 4000 mg/kg and is based on a four dose study using four animals per group (19). This is supported by an industrial toxicology report that states the oral rat LD50 is >3200 mg/kg (20). Although these studies do not meet the current OECD guidelines, the quality is sufficient to provide a good estimate of the acute oral toxicity of Monoglyme. In addition, the result is in accord with data for many other similar glycol ethers that are known to have low acute toxicity.

**Inhalation Exposure**

The acute inhalation toxicity of Monoglyme was determined in a two-dose study in which the six-hour inhalation LC50 was found to be between 20 and 63 mg/L. The vapors produced some irritation and anesthesia at the high level. All high dose animals survived the exposure but died within 72 hours post-exposure (21).

**Summary and Recommendation for Acute Toxicity**

The oral and inhalation acute toxicity of Monoglyme are satisfactorily established to meet the requirements of the HPV Challenge Program. No additional testing is recommended.

## Repeat Dose Toxicity

Information on the repeated-dose effects of Monoglyme is derived from an understanding of the metabolic conversion of Monoglyme to metabolites in test animals. Although direct chemical evidence identifying the primary and secondary metabolites of Monoglyme was not found, the metabolic pathways for this class of chemicals are well known. Additionally, there is very strong biological evidence linking adverse effects of Monoglyme with a common active metabolite of methoxy glycol ethers.

It has been demonstrated that most of the toxic effects of the monoalkyl glycol ethers arise as a result of the metabolic conversion of the glycol ether into a substituted acetic acid derivative. In Figure 1, this pathway is shown for the prototype, and most toxic, of the family members 2-methoxyethanol. Upon absorption, at least three paths compete for the test material. Excretion by the lungs or kidneys accounts for a small portion of the absorbed dose. Demethylation by mixed-function oxidases, a relatively slow reaction, accounts for some metabolic conversion to ethylene glycol which is converted to oxalate. Dehydrongenase enzymes initially convert the free alcohol to the aldehyde and then the carboxylic acid (22). This is a very rapid conversion (as indicated by the size of the arrows) and it is known that a teratogenic dose of 2-methoxyethanol is completely oxidized in a period of one-hour in rats (ref, Sheets). The competing reaction, demethylation of -ME to ethylene glycol is comparatively slow as it is accomplished by the mixed-function oxidase system. The pharmacokinetics of these transformations have been determined in the rat and the approximate ratio of production for 2-methoxyacetic acid:ethylene is 5:1. The relative first-order rate constants have been determined to be 31 L/h/kg liver for conversion of 2-ME to 2-methoxyacetic acid and 5.6 L/h/kg liver for conversion of 2-ME to ethylene glycol (23). There is some question as to what is the active form of 2-methoxyacetic acid that interferes with metabolism, but there is general agreement that 2-methoxyacetic acid is the proximate toxin. It is also established the clearance of 2-methoxyacetic acid is relatively slow as compared to its formation and the clearance in man may be much longer than in rats (24).

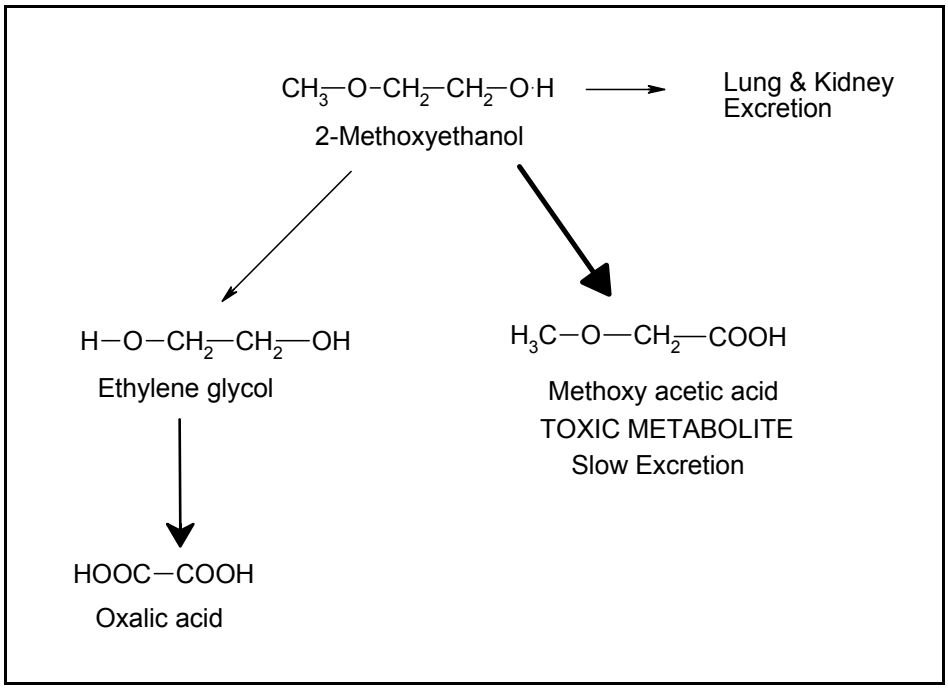



**Figure 1. Metabolism of 2-Methoxyethanol into Methoxy Acetic Acid.**

The anticipated metabolic pathway for Monoglyme is shown in Figure 1. Although definitive chemical evidence for the metabolism of Monoglyme to 2-ME was not found in the open literature, the biological evidence for this conversion is strong. One study of pregnant mice in particular compared four glycol ethers at a dose of 4 mmol/kg: ethylene glycol monomethyl ether (2-ME 304 mg/kg), ethylene glycol dimethyl ether (Monoglyme, 361 mg/kg), diethylene glycol dimethyl ether (537 mg/kg), and triethylene glycol dimethyl ether (713 mg/kg). Fetuses were collected on gestation day 18 and examined. There were no signs of maternal toxicity, and intrauterine survival was unaffected by glycol ether treatments. Fetal body weights were significantly reduced only in litters treated with Monoglyme. There was no treatment-related pattern of gross external malformations other than paw defects. Paw defects were present in 87.5% of 2-ME-treated litters (68.5% of fetuses) and 86.7% of Monoglyme-treated litters (33.8% of fetuses). Hindpaw defects predominated over forepaw, with syndactyly the most common malformation. The incidences of oligodactyly and short digits were also significantly increased. The similarity of malformations produced by these methyl-substituted glycol ethers is proposed to be attributable to *in vivo* conversion to a common teratogen, methoxyacetic acid. (25)

Additional evidence for a mixed-function oxidase production of 2-ME from Monoglyme comes from an *in vitro* study of microsomal oxidation of Diglyme in which it was demonstrated that microsomal cytochrome P-450 oxidizes Diglyme to 2-ME and 2-(2-methoxyethoxy)ethanol.

Both human and rat liver microsomes were demonstrated to catalyze the oxidation of Diglyme (26).

This information about the metabolic pathways and nearly identical developmental effects at similar dose levels indicates that the repeated-dose, reproductive, and developmental toxicity of Monoglyme can be ascertained from the results of these studies on 2-ME in the appropriate protocol. A slight adjustment for dose due to molecular weight and pulmonary/kidney may be necessary but the spectrum of effects and dose-response should be similar. The presence of excess Monoglyme in the body is also expected to inhibit the conversion of 2-ME to ethylene glycol, a process that could increase the relative yield of 2-methoxyacetic acid from Monoglyme. Although the relative pharmokinetics of metabolism are somewhat speculative, the similarity in effects and dose levels for the Chernoff-Kavlock screen, the paw defects in mice, and the perinatal toxicity in rats (27) strongly argue that 2-ME is an excellent surrogate for repeated dose toxic effects of Monoglyme.

**Oral Exposure**

A great deal of information is available on the repeated-dose toxicity of the biologically indicated metabolite of Monoglyme, 2-methoxyethanol (2ME). One of the more definitive repeated dose studies was conducted on rats and mice by the National Toxicology Program using the drinking water route and reported in 1993 (28). In this study testicular degeneration was a prominent finding in rats even at the lowest dose tested (750 ppm, about 70 mg/kg/day) and in females, at this level, thymic atrophy was a finding. Thus, a NOEL was not found for rats of either sex. In the case of mice, the NOAEL for testicular degeneration and increased hematopoiesis in the spleen was 2000 ppm in males. A NOAEL was not reached for female mice since adrenal gland hypertrophy and increased hematopoiesis in the spleen occurred at the lowest concentration administered (2000 ppm, about 300 mg/kg/day).

Repeated dose exposure in the drinking water was also associated with progressive anemia in rats and mice and increased mortality in rats at the two highest doses. The target organs can be identified as testes, bone marrow, spleen (hematopoiesis), thymus and adrenal. In general, the testes is considered a sensitive, if no the most sensitive, target organ.

Regarding extrapolation to man, the standard use of the safety-factor approach is somewhat confounded by the differences in pharmacokinetics (especially the long excretion half-life of 2-methoxyacetic acid in man) and the seriousness of the most sensitive target tissue. There is, however, a more definitive manner to assess human exposure and potential risk using the biological indicator approach. It is established that 2-methoxyacetic acid is the defining toxic metabolite and studies have shown that the level of 2-methoxyacetic acid in urine is an excellent

marker for exposure. The reference value for this metabolite has not been firmly set; however, the BEI reference level for Monoglyme should be as protective as the reference level for 2-ME.

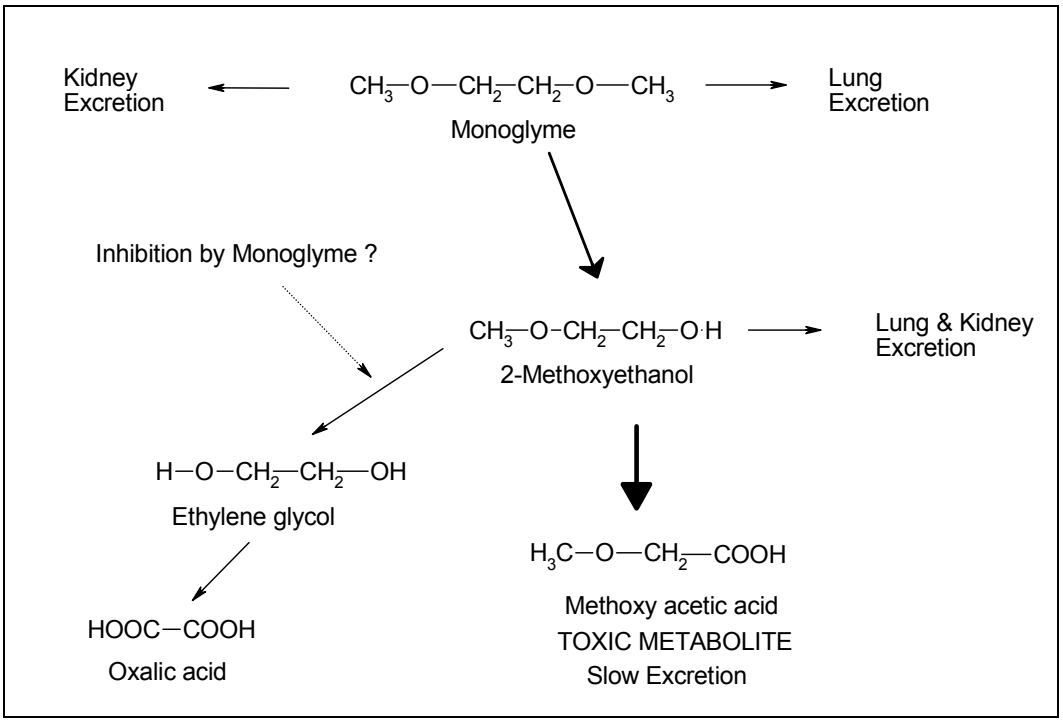



**Figure 2. Major Metabolic Pathways for Monoglyme**

**Summary and Recommendations for Repeated-Dose Toxicity**

Based on common metabolites and biological indications of similar mechanism-specific adverse effects, the repeated dose toxicity of Monoglyme is approximated quantitatively and qualitatively by the studies on 2-methoxyethanol. 2-ME and hence Monoglyme, are potent testicular toxins, adversely affect the bone marrow, cause thymic atrophy and affect the adrenals. No additional testing is recommended as the target organs are understood on the basis of the metabolic product 2-methoxyacetic acid. Exposures and relative risk to humans may also be determined by using the Biological Exposure Indicator 2-methoxyacetic acid that can be used with the same reference range as for 2-ME.

# Genetic Toxicity

The SIDS/HPV requirement for genetic toxicity screening is for two end-points: generally one sensitive to point mutation and one sensitive to chromosomal aberrations. In the case of this material, these requirements are basically fulfilled by OECD guideline-like studies. The data indicate genotoxic activity *in vitro* and suggest the potential for *in vivo* genotoxic activity.

**Genetic Toxicology *in vitro***

A *S. typhimurium* reverse mutation assay is cited by the National Toxicology Program as "positive" no other information is available in the open literature for this study result (29). In the NTP Results report (12-2001 version) ethylene glycol diethyl ether is also listed as positive in the Ames test. Monoglyme is known to be cytotoxic to Salmonella typhimurium (30) at concentrations as low as 500 microliters per plate. McGregor also notes in this paper that most glycol ethers have low activity in the Ames test.

Mammalian cell point mutation activity was assessed using the HGPRT assay in CHO cells. In this study Monoglyme produced no evidence of genotoxicity in the presence or absence of S9 metabolic activation (31, robust summary attached). Although no guideline was specified, the study was conducted in accord with OECD 476 *In Vitro* Mammalian Cell Gene Mutation (32).

Clastogenic activity was assessed *in vitro* using the Sister Chromatid Exchange in Chinese Hamster Ovary Cells Test (SCE). In this test, the material produced numerous indications of statistically significant effects on the frequency of SCE over the range of concentrations tested with and without addition of an active S9 metabolic system. A high number of cells were also observed with significant types of chromosomal aberrations suggesting that material was a clastogenic agent, especially in the presence of S9 activation (33, robust summary attached). No specific guideline was specified for the study; however, it was conducted in accord with OECD 479 "Genetic Toxicology: *In vitro* Sister Chromatid Exchange Assay in Mammalian Cells" (34).

DNA damage was assessed using an *in vitro* unscheduled DNA synthesis (UDS) Assay. In this assay, rat hepatocytes were treated with a wide range of concentration of Monoglyme up to concentrations demonstrating cytotoxicity in the assay system. Treatment did not produce either statistically significant or dose-related increases in the amount of UDS activity as measured by radioactive thymidine uptake. Activity was measured by liquid scintillation counting of nuclear preparations and also by counting of nuclear DNA (35, robust summary attached). The protocol was conducted in accord with OECD 482 guidelines (36) with regard to most experimental parameters. The number of replicates was fewer than recommended by the guideline and there

was no independent repeat; however, more concentration levels were tested than typical and there was an independent radioactivity determination of nuclear DNA.

**Summary of Genetic Toxicology and Recommendations:**

Strictly speaking, the SIDS requirement for genetic testing has been met as both a point mutation and an assay sensitive to clastogenic effects have been conducted using an acceptable protocol. This also is in accord with the more recent guidance from the EPA concerning the HPV Program genotoxicity guidelines encouraging reduction in live animal use (October 14, 1999 letter from EPA to sponsors). In the case of Monoglyme, the results have been mixed using several *in vitro* studies. Sufficient information is available for Monoglyme for the purposes of the HPV Challenge Program. No further testing is recommended.

## Reproductive Toxicity

Monoglyme is considered to be a reproductive toxin based on its metabolism to 2-methocyacetic acid which is an established testicular toxin (see repeated dose section). Adverse effects on the conceptus, including embryo lethality are also caused by this metabolite. Direct specific effects on female reproduction are not known to result from 2-methoxyacetic acid and thus are not expected from Monoglyme exposure

**Summary and Recommendation for Reproductive Toxicity**

The extensive literature on 2-methoxyethanol (2-ME) and the metabolic data indicating that Monoglyme's oxidative metabolism to 2-methoxyacetic acid indicates a clear and significant repeoductive hazard from overexposure to Monoglyme. The available information is sufficient for the purposes of the EPA HPV Challenge Program. No additional testing is recommended.

## Developmental Toxicity

Studies of the developmental toxicity and perinatal effects of Monoglyme are available from the open literature. In a study conducted by oral gavage at 0, 30, 60, 120, 250 or 1000 mg/kg, groups of pregnant female rats were treated from day 8 to 18 of gestation (37). The results show that 120 mg/kg/day or more was associated with 100% fetal death and doses of 30 or 60 mg/kg were fetotoxic but did not produce major malformations (see robust summary for details). This study suggests that Monoglyme is a specific developmental toxin as would be anticipated based on its metabolism to 2-methoxy acetic acid.

This result in rats is strikingly similar to the results Stenger et al. (38) reported in 1971 for 2-ethoxyethanol. In this study of 2-ethoxyethanol, groups of 20 pregnant rats were treated orally at 0, 11, 23, 46.5, 93, 186, or 372 mg/kg per day from gd 1 through gd 21. A significant increase in embryonic and fetal deaths occurred in rats treated at 46.5 mg/kg per day and higher, at oral doses of 93 to 372 mg/kg per day, the incidence of skeletal aberrations increased in a dose related pattern (no statistical treatment given). Complete resorption occurred at 372 mg/kg. No comparable rat gavage studies could be found for 2-ME. 2-Ethoxyethanol is known to be very similar in its effects but less potent than 2-ME (39); thus, the similarity of the effects of Monoglyme and 2-ethoxyethanol add strength to the argument that Monoglyme is metabolized to 2-methoxyacetic acid. The relative potencies (Monoglyme caused 100% fetal death at 120 mg/kg/day while 2-ethoxyethanol caused 100% death at 372 mg/kg/day) support the metabolism of Monoglyme to 2-methoxyacetic acid which is known to be more potent than 2-ethoxyacetic acid (the active metabolite of 2-ethoxyethanol)(39).

A mouse teratology study with oral doses of 0, 250, 350, or 490 mg/kg on days 7 to 10 of gestation produced results indicating teratogenicity and fetotoxicity (40). In this study, there was an increased incidence of major malformations including exencephaly, open eye, and tail defects at the two highest doses (see robust summary for details). Clear evidence showing lack of maternal toxicity is not presented in the publication.

The mouse teratology result is similar to the results Nagano et al. reported in 1981 for 2-ME after oral gavage in the mouse (41). In this study of 2-ME, 1000 mg/kg produced total resorptions, 250 or 500 mg/kg produced increased fetal deaths, 125 or 250 mg/kg was associated with gross fetal abnormalities and skeletal malformations, 62.5 mg/kg produced only skeletal malformations and 31.25 mg/kg was fetotoxic with retarded ossification. Thus it appears that Monoglyme is a less potent developmental toxin in the mouse than 2-ME, which is the predicted result based on the metabolic pathway and slow conversion of Monoglyme to 2-ME competing with excretion.

The lower potency of Monoglyme as compared to 2-ME in producing paw defects was also demonstrated in a study discussed earlier, in which pregnant mice dosed at 4 mmol/kg 2-ME or Monoglyme showed paw defects in 87.5% of 2-ME-treated litters (68.5% of fetuses) and 86.7% of Monoglyme-treated litters (33.8% of fetuses) indicating a lower potency for Monoglyme (25).

**Summary and Recommendation for Developmental Toxicity**

Rat and mouse developmental toxicity studies of Monoglyme indicate that is has the potential to be teratogenic and fetotoxic and may cause delayed partition. Although the studies available are not GLP and do not clearly establish the A/D ratio, they show a dose-response relationship and

indicate the potency range for Monoglyme as a developmental toxin in rats and mice. Sufficient information is available for Monoglyme for the purposes of the HPV Challenge Program. No further testing is recommended.

## Conclusions

With regard to the parameters specified in the EPA HPV Challenge program, the available information from laboratory experiments, surrogate chemicals and modeling efforts fill all of the HPV Program requirements for chemical parameters and toxicity information.

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